

Sub C1

82. The synthetic tissue of claim 79, wherein the recipient and the mammal are the same individual.

83. The synthetic tissue of claim 79, wherein substantially all of the neuronal progenitor cells in the synthetic tissue are capable of differentiating into only a single type of neurons selected from the group consisting of dopaminergic, cholinergic, GABAergic, and serotonergic neurons upon contact of the synthetic tissue with a differentiation-promoting factor, wherein the synthetic tissue is made by selecting and proliferating a single neuronal progenitor cell after contacting the progenitor cells and the differentiation-promoting factor, wherein the single progenitor cell is selected on the basis that it expresses a marker characteristic of the selected type of neuron.

84. The synthetic tissue of claim 83, wherein the single neuronal progenitor cell is proliferated by contacting the cell with a mitogen after selecting the cell. --

REMARKS

Claims 44-84 are pending in this application upon entry of this Amendment. Claims 26-43 have been cancelled without prejudice. Claims 44-84 have been added. Claims 44, 63, and 79 are the only independent claims. Each of the newly-added claims is supported in the specification, as indicated in the following section.

Support in the Specification

New independent claims 44 and 79 designates the claimed composition of matter a "synthetic neuronal tissue," as disclosed in the specification, for example at page 1, lines 26-30, and at page 2, lines 15-17. The claim indicates that the tissue can be derived from neuronal tissue taken from either the brain or the spinal cord of a mammal, as disclosed, for example at page 2 lines 21-24. The tissue comprises neuronal progenitor cells that are partially differentiated, as disclosed, for example at page 3, lines 12-14, in the sense that the progenitor cells are able to differentiate substantially only into a single type of dopaminergic, cholinergic, GABAergic, and serotonergic neurons (see page 2, lines 15-17) when they are contacted with a differentiation-promoting factor, as disclosed, for example at page 3, lines 22-25. Claimed characteristics of the synthetic neuronal tissue are that it does not comprise enough glial cells to

elicit an immune response in a transplant recipient as disclosed, for example at page 2, lines 11-14, and that the progenitor cells therein maintain the ability to perform mitosis as disclosed, for example at page 5, lines 10-12.

Synthetic tissues comprising certain levels of partially differentiated neuronal progenitor cells (as recited in new claims 45, 46, and 70) are disclosed, for example at page 2, lines 17 and 18.

New claims 47-51 recite that the mammal from which neuronal progenitor cells is obtained can be an adult or embryonic human cells, such as those obtained from umbilical cord blood or subventricular or hippocampal brain regions, as disclosed, for example at page 2, lines 21-33. New claim 52 recites use of a monoclonal cell line, as disclosed, for example at page 7, line 20, through page 9, line 21.

New claims 53-57 and 83 recite that the progenitor cells can be treated so as to differentiate the progenitor cells into substantially only a particular type of neuron as disclosed, for example at page 3, lines 22-25, and at page 5, lines 1-16.

New claims 58-62 and 64-69 recite various differentiation-promoting factors disclosed in the specification, for example at page 2, line 4-9, page 5 lines 2-9 and 24-33, and page 6, lines 1-16.

New claims 63, 71, and 78 recite a synthetic tissue made by a process described throughout the specification, for example at page 4, lines 1-12, optionally using sub-atmospheric oxygen levels.

New claims 72-77 recite use of sub-atmospheric oxygen levels in various parts of the methods as described, for example at page 4, lines 20-34.

New claims 80 and 81 recite that the progenitor cells are partially differentiated by contacting them transiently with a factor as described, for example at page 5, lines 2-12.

New claim 84 recites use of a mitogen to expand a sub-cloned, partially-differentiated neuronal precursor cell as disclosed, for example at page 7, line 20, through page 9, line 19.

For the foregoing reasons, the Applicant respectfully contends that the new claims do not include new matter.

Restriction Requirement

The Examiner's comments in item 1 of the Office Action are not understood by the Applicant and are believed to be irrelevant. The claims do not recite differentiated dopaminergic neurons, nor are such neurons separately claimed.

The Applicant believes that each of pending claims 44-84 corresponds to elected Group I.

Objections to Claims

The Examiner objected to claims 29, 30, 32-35, 38, 39, and 42 in item 2 of the Office Action on the grounds that each of these claims failed to limit the claim from which it depended. Each of these claims has been canceled, and the Applicant believes that none of the presently pending claims is in improper dependent form. This objection is therefore believed to be moot.

In item 3 of the Office Action, the Examiner objected to claim 37 on account of spelling errors. Claim 37 has been canceled, and the Applicant believes that the presently-pending claims do not contain spelling errors. This objection is therefore believed to be moot.

Rejection of Claims Pursuant to 35 U.S.C. § 112, First Paragraph

Claims 26-43 stand rejected pursuant to 35 U.S.C. § 112, first paragraph. It is not clear from the Office Action whether the Examiner's rejection is based on alleged failure of compliance with the written description requirement, on the prohibition of addition of new matter to an application, or on both of these grounds. The Examiner cites several reasons for this rejection.

With regard to claims 27 and 35, the Examiner objected to the alleged lack of antecedent basis for the ">90%" recitation. Claims 27 and 35 have been canceled, and this aspect of the rejection is believed to be moot. Newly added claims 45, 46, and 70 presently include percentage recitations. However, each of these newly added claims is believed to have proper antecedent basis, since each recitation refers to the "partially-differentiated neuronal progenitor cells" recited in the corresponding base claim. As noted above, synthetic neuronal tissues comprising >90% or >95% partially differentiated neuronal progenitor cells (as recited in new claims 45, 46, and 70) are disclosed, for example at page 2, lines 17 and 18. Thus, each

of claims 45, 46, and 70 has proper antecedent basis, and none of these claims includes subject matter that was not described in the application as filed.

With regard to claim 36, the Examiner objected to recitation of repetition of one of the three steps listed in that claim. Claim 36 has been canceled, and this aspect of the rejection is believed to be moot. Newly added claim 71 recites repetition of a partial differentiation step recited in new claim 63. This is not believed to be improper, because the specification discloses that this partial differentiation (or "priming") step can be repeated (e.g., at page 5, lines 14-16 of the specification).

With regard to claim 41, the Examiner objected to recitation of "conditions simulating induced oxygen content." Claim 41 has been canceled, and this aspect of the rejection is believed to be moot. Newly added claims 75 and 77 recited conditions which simulate reduced atmospheric oxygen content, as disclosed in the specification, for example at page 4, lines 8-11.

With regard to claim 31, the Examiner objected to recitation of the phrase "being adapted for transplantation to restore neuronal deficits." Claim 31 has been canceled, and this aspect of the rejection is believed to be moot. The phrase used in claim 31 does not occur in any of the pending claims.

For the foregoing reasons, the Examiner's rejection of claims 26-43 pursuant to 35 U.S.C. § 112, first paragraph is believed to be inapplicable to the presently pending claims. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection of Claims Pursuant to 35 U.S.C. § 112, Second Paragraph

Claims 26-43 stand rejected pursuant to 35 U.S.C. § 112, second paragraph. The Examiner cites several reasons for this rejection.

With regard to claim 26, the Examiner objects to the phrase "not containing any physiologically active amounts of immunocompetent glial cells." Claim 26 has been canceled, and this phrase is not used in any of the pending claims. Instead, new independent claims 44, 63, and 79 recite that the synthetic tissue "does not comprise sufficient glial cells to provoke an immune response upon implantation of the synthetic tissue into a recipient." The Applicant contends that the skilled artisan is aware of the immunogenic nature of glial cells (e.g., as disclosed in the specification at page 1, lines 18-20, and page 2, lines 11 and 12) and of methods of assessing the immunogenicity of a composition. The Applicant has taught how to

make synthetic neuronal tissue preparations that contain sufficiently few (or no) immunogenic glial cells that the tissue does not induce an immune response when it is implanted. The language used in the claim is simply the nearest the words of the English language can come to precisely defining what the Applicant has invented. The Applicant respectfully contends that the skilled artisan would have no doubt with regard to the metes and bounds of the phrase used in claim 44, and the Examiner is requested not to repeat the rejection of claim 26 pursuant to 35 U.S.C. § 112, second paragraph, for the newly added claims.

The Examiner suggests that (glial) "[c]ells either invoke an immune reaction or they do not" (Office Action, page 4, final sentence of second paragraph). The Applicant respectfully suggests that this statement is an over-simplification of immune function. As indicated in the highlighted portion of the enclosed reference (Parslow) from a medical immunology text, whether or not a substance (such as a glial cell) will evoke an immune response depends on the dosage of the substance that is administered. There is a threshold effect, whereby low levels of an immunogen will evoke no immune response in a subject unless a threshold dosage is administered. The Applicant has discovered synthetic neuronal tissue compositions (and methods of making them) which contain so few glial cells that they do not meet this immunogenic threshold and do not evoke an immune response when they are implanted into a recipient. In many instances, it will not be possible to know whether the claimed synthetic neuronal tissue contains absolutely no glial cells or merely so few glial cells that an immune response is not provoked. Either way, the result is the same - no immune response occurs. The Applicant is not required to know why this characteristic of the claimed compositions occurs - it is sufficient that it does occur and is recited in the claims. For this reason, the Applicant respectfully contends that there is nothing indefinite about reciting in independent claims 44, 63, and 79 that the claimed tissue does not comprise enough glial cells to elicit an immune response.

With regard to claims 26, 27, 34, 35, and 42, the Examiner objects to the terms "tissue material," "differentiating promoting factor," and "exogenous factors." Each of the rejected claims has been canceled. The terms "tissue material" and "exogenous factors" are not used in the presently pending claims, so the Examiner's objection to those two terms is moot. Several pending claims (e.g., 54-69 and 81) recite a "differentiation-promoting factor." The Examiner contends that the metes and bounds of this term are "unknown and ambiguous" because these factors are not specifically recited. The Applicant respectfully contends that

numerous factors are known that are useful for promoting differentiation of neuronal progenitor cells - including those disclosed in the specification at page 5, line 18, through page 6, line 16. The identity of the factor is not important. What is important is that the factor promote differentiation of the neuronal progenitor cells recited in the claims, but not to such a degree that the progenitor cells lose their ability to proliferate (i.e., to "perform mitosis," as recited in the claims). The skilled artisan would therefore not have any difficulty defining the metes and bounds of the term "differentiation-promoting factor."

With regard to claim 27, the Examiner objects to recitation of an "issue" in that claim. Claim 27 has been canceled, and no presently pending claim recites an "issue." This objection is therefore moot.

In item 6 of the Office Action, the Examiner rejects claims 31-46 based on the Examiner's objection to the phrase "being adapted for transplantation...". The Applicant assumes that this rejection was intended to apply to claims 31-43, claims 44-46 not having been pending at the time the Office Action was issued. The rejected claims have been canceled, and this phrase is not used in any of the presently pending claims. This aspect of the Examiner's rejection is therefore moot.

Also in item 6, the Examiner objects to the language of claim 34, on the grounds that the language is confusing. Claim 34 has been canceled, and the claims have been re-written in a more idiomatic fashion. This aspect of the Examiner's rejection is therefore believed to be moot. Nonetheless, the Applicant wishes to comment on a statement made by the Examiner. In the final sentence of the third paragraph of item 6, the Examiner asserts that "cells are either differentiated, or they are not." Although the Applicant recognizes that the context in which the statement was made does not necessarily relate to the presently pending claims, the Applicant wishes to remind the Examiner that the situation is not this simple.

As with most types of progenitor cells, neuronal progenitor cells have multiple states (or degrees) of differentiation. In general, progenitor cells initially are able to differentiate to become a wide variety of cell types. As the progenitor cells become increasingly differentiated, the variety of types a cell can become decreases. However, this differentiation process is not the 'yes-or-no' state that the Examiner's comment suggests. Instead, a progenitor cell might initially be able to become any of ten cell types; as it differentiates, it may remain capable of becoming any of only five of those types; later, perhaps only two, and finally it can become a cell of only a single type (i.e., it becomes terminally

differentiated). At some point, differentiated cells lose the ability to perform mitosis (i.e., to proliferate).

The Applicant has discovered that (and how) neuronal progenitor cells can become relatively highly (or even substantially terminally) differentiated before they lose the ability to mitose. The specification teaches how to make partially-differentiated (or substantially terminally differentiated) neuronal progenitor cells that retain the ability to proliferate. These proliferation-competent, partially-differentiated neuronal progenitor cells can be sub-cloned and expanded to provide a brain tissue suitable for implantation into recipients. For this reason, the pending claims recite "partially-differentiated neuronal progenitor cells" that have the capability to perform mitosis. The Applicant respectfully contends that there is nothing improper about describing neuronal progenitor cells as "partially-differentiated," particularly where, as here, the characteristics of those cells are recited in the claims.

The Examiner rejects claims 36 and 39 for lack of antecedent basis for certain terms. These claims have been canceled, and the Applicant does not believe that any pending claim raises the same issue. This aspect of the rejection is therefore believed to be moot.

For the foregoing reasons, the Examiner is respectfully requested to reconsider and withdraw the rejections of (canceled) claims 26-43 pursuant to 35 U.S.C. § 112, second paragraph, and not to apply these rejections to new claims 44-83.

Rejection of Claims Pursuant to 35 U.S.C. § 102(b) in View of Boss

Claims 26-43 were rejected pursuant to 35 U.S.C. § 102(b) in view of Boss et al. (USPN 5,411,883). In the Examiner's view, Boss discloses isolated mammalian neuronal progenitor cells that meet the recitations made in the claims. The Examiner suggests that Boss discloses evidence of identity between the cell preparation disclosed therein and the claimed composition, and that the absence of evidence to the contrary indicates that the Boss cell preparation meets several recitations in the rejected claims. Claims 26-43 have been canceled. The Applicant respectfully disagrees with the Examiner's assessment of the relevance of Boss and requests that the Examiner not reject the newly added claims in view of Boss.

As an initial matter, the Applicant reminds the Examiner that the Examiner bears the burden of proving that a cited reference anticipates a claim pursuant to 35 U.S.C. § 102(b). M.P.E.P. § 2112. *In re Oelrich*, 212 U.S.P.Q. 323 (C.C.P.A. 1981). *Ex parte Levy*, 17

U.S.P.Q.2d 1461 ("In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art"). The Applicant believes that the Examiner has improperly relied on unsupported assertions of purportedly inherent properties of the cell preparation disclosed in Boss. This point may be irrelevant, however, since Boss discloses information that indicates that the cell preparation disclosed therein is not the synthetic neuronal tissue that is recited in the pending claims, as discussed in the following paragraph.

Boss discloses (column 13, lines 66-68) that the cells in the preparation disclosed therein cease proliferation after the differentiation treatment to which those cells are subjected. In contrast, the partially-differentiated neuronal progenitor cells in the claimed compositions retain the ability to proliferate, as disclosed in the specification, for example at page 5, lines 10-14 (and as explicitly recited in newly added claim 79). Proliferative ability of the progenitor cells in the claimed composition is also recited in the claims (i.e., the progenitor cells "maintain their capability to perform mitosis," as recited in independent claims 44 and 63; independent claim 79 recites that treatment of the progenitor cells does not eliminate their capability to perform mitosis). This difference indicates that the cell preparation made by Boss does not comprise the partially-differentiated neuronal progenitor cells recited in each of the pending independent claims. For the foregoing reason, the Applicant requests that the Examiner reconsider the rejection of claims 26-43 pursuant to 35 U.S.C. § 102(b) in view of Boss, and that the Examiner not apply this rejection to newly added claims 44-84.

Rejection of Claims Pursuant to 35 U.S.C. § 102(b) in View of Luskin

Claims 26-43 were rejected pursuant to 35 U.S.C. § 102(b) in view of Emory University/Luskin (WO 97/02049; "Luskin"). In the Examiner's view, Luskin discloses neuronal progenitor cells that satisfy the recitations of the rejected claims. The Applicant respectfully disagrees with the Examiner's assessment of the relevance of Luskin and requests that the Examiner not reject the newly added claims in view of Luskin.

Luskin discloses (e.g., in the abstract and at page 4, lines 2-6) that the neuronal progenitor cells in the composition disclosed therein express a neuron-specific marker. However, those progenitor cells can differentiate to become any of a variety of types of neuron cells. For example, in the abstract, at page 7, lines 15-18, and at page 8, lines 9-12, Luskin

discloses that the neuronal progenitor cells that can give rise to progeny cells which are able to differentiate into various types of neuronal cells. In contrast, the pending claims recite that the neuronal progenitor cells in the claimed synthetic neuronal tissue are able to differentiate substantially into only a single type of neuronal cell. For this reason, Luskin does not anticipate the claimed compositions.

For the foregoing reason, reconsideration of the rejection of canceled claims 26-43 pursuant to 35 U.S.C. § 102(b) in view of Luskin is requested, and the Examiner is further requested not to apply this rejection to newly added claims 44-84.

Summary

For the foregoing reasons, the Applicant believes that each of pending claims 44-84 is in condition for allowance. Reconsideration and withdrawal of the Examiner's objections and rejections are respectfully requested. In the event the Examiner believes that minor or merely formal changes would place the claims in condition for allowance, the Examiner is requested to contact the Applicant's undersigned representative by telephone.

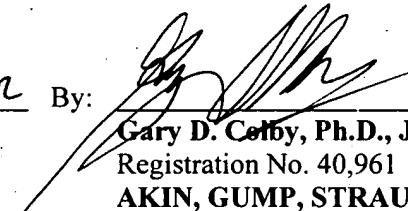
Respectfully submitted,

HORST PESCHEL

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(Date)

By:


Gary D. Colby, Ph.D., J.D.

Registration No. 40,961

AKIN, GUMP, STRAUSS, HAUER & FELD, L.L.P.

One Commerce Square

2005 Market Street - 22nd Floor

Philadelphia, PA 19103-7086

Telephone: 215-965-1200

Direct Dial: **215-965-1285**

Facsimile: 215-965-1210

E-Mail: gcolby@akingump.com

Enclosures: Petition for a One-Month Extension of Time
Copy of Stites et al., 1997, Medical Immunology, 9th Ed., Appleton & Lange,
Stamford Connecticut, pp. 74-75.